

# ABCC GRID Promoter TFSite Comparison Page to find shared regulatory elements for co-regulated genes in toxicology

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## BACKGROUND

Toxicological studies often yield lists of genes potentially co-regulated based on coordinate expression changes. Three examples demonstrate that new hypotheses and research directions can be proposed by identification of potential transcription factor binding sites shared among a group of genes, the service the web page provides. Use in toxicological dose-response gene expression studies and similar treatment-response experimental paradigms is discussed, including limitations of the application.

## WEB TOOL

The screenshot shows the 'ABCC GRID Promoter TFSite Comparison Page' with a form for inputting a list of genes and selecting various options for the comparison. The form includes fields for 'Input Promoter List Source', 'Promoters to Compare', 'TF Site Probability', 'TF Site Strandedness', 'TF Site Match', 'Output Feature', 'Output Style', 'Output Probability Column', 'Output Sites (R3) Column', 'Output Factors Column', 'Output DB Source Row', 'Output Gene Name Row', 'Output mRNA Access Row', 'Free TF Sites/REs', and 'Show Run Report'. A list of results is shown on the right, including gene names, accession numbers, and TF site matches.

Figure 1. Quick Results Example of Website page for Promoter Analysis. Users can access the website, paste in their favorite gene list and, using the options shown, promptly have a list of potential transcriptional regulatory sites common to the submitted genes.

Table 1. Genes reported to be Hif1 $\alpha$ -regulated used for validating Transcription Factor Analysis.

Gene Product	Transcription Factor	UniGene	Name	RefSeq ID
Adenylate kinase 3	HIF-1	196,211,700	AK3	NM_010332
A1B-Adrenergic receptor	HIF-1	196,410,131	ADORA1B	NM_000679
Adrenomedullin	HIF-1	196,44,1047	ADM	NM_001124
Aldehyde A	HIF-1	196,22,3415	ALDOA	NM_000334
Aldehyde C	HIF-1	196,15,247	ALDOC	NM_005165
Carbonic anhydrase-9	HIF-1	196,63,827	CA9	NM_001216
Ceruloplasmin	HIF-1	196,35,013	SLC22A7	NM_002832
Cytochrome P-450	HIF-1	196,190,354	PTGS2	NM_000963
Endothelin-1	HIF-1	196,51,1899	EDN1	NM_001956
Enkephalin	HIF-1	196,43,3456	ENK1	NM_001428
Erythropoietin	HIF-1	196,23,03	EPO	NM_000789
GADD153	Not determined	196,13,5406	CEBP2	NM_005762
Glucose transporter-1	HIF-1	196,16,992	SLC2A1	NM_006416
Glucose transporter-3	HIF-1	196,41,925	SLC2A3	NM_006931
Glyceraldehyde-3-phosphate dehydrogenase	HIF-1	196,16,926	GAPD	NM_002046
Heme oxygenase-1	HIF-1	196,20,283	HMOX1	NM_002133
Headcase-1	HIF-1	196,11,062	HC1	NM_001189
Headcase-2	HIF-1	196,40,260	HC2	NM_001189
Insulin-like growth factor-2 (IGF-2)	HIF-1	196,34,010	IGF2	NM_000812
IGF-binding protein-1	HIF-1	196,40,1316	IGFBP1	NM_000590
IGF-binding protein-2	HIF-1	196,43,3326	IGFBP2	NM_000597
IGF-binding protein-3	HIF-1	196,40,223	IGFBP3	NM_000598
Interleukin-6	HIF-1	196,51,2248	IL6	NM_000600
Lactate dehydrogenase A	HIF-1	196,22,65	LDOA	NM_000566
Nitric oxide synthase-2	HIF-1	196,19,3768	NOS2A	NM_000625
NBP3	HIF-1	196,24,48	NBP3	NM_004052
Ornithine decarboxylase	Not determined	196,44,3459	ODC1	NM_002539
P21	Not determined	196,37,072	CDKN1A	NM_004404
P27	Not determined	196,23,599	CDKN1B	NM_004064
P35	Not determined	196,35,013	CDKN1C	NM_003895
Phosphofructokinase L	HIF-1	196,30,741	PFKL	NM_002626
Phosphoglycerate kinase-1	HIF-1	196,31,771	PFKB1	NM_000291
Plasminogen activator inhibitor-1	HIF-1	196,41,1925	SEPRIN1	NM_000602
Prolyl-4-hydroxylase $\alpha$ (1)	HIF-1	196,27,1224	PH-4	NM_177939
Pyruvate kinase M	HIF-1	196,19,016	PKM2	NM_000654
Tissue factor	HIF-1	196,62,192	F3	NM_001993
Transformin	HIF-1	196,43,2923	TF	NM_001983
Transformin receptor	HIF-1	196,102,748	TRFR	NM_003334
Transforming growth factor $\beta$ 3	HIF-1	196,20,225	TGF $\beta$ 3	NM_003239
Triphosphate isomerase	HIF-1	196,21,1271	TFPI	NM_000365
Tyrosine hydroxylase	HIF-1	196,43,5609	TH	NM_000360
Vascular endothelial growth factor (VEGF)	HIF-1	196,23,193	VEGF	NM_003376
VEGF receptor FLT-1	HIF-1	196,34,7713	FLT1	NM_002019

For Table 1, Hif1 $\alpha$ -regulated genes all exhibited Hif-response elements in their promoter regions except one found only in mice. For Table 2, groups of genes expressed could be compared both between subclones and between temporal patterns. For Table 3, two chemical treatments that induce differentiation through different means exhibit slight variations in regulatory elements reported.

## APPLICATIONS

Table 2. Regulatory elements common within chronosequential gene expression patterns. N.B.: Minus U937 subclone at left; Plus subclone at right. U = up > 2-fold, D = down > 2-fold over the intervals 0-6, 6-24, and 24-48 hrs.

Table 3. Regulatory elements comparing two differentiation agents for genomic response down-regulated at 6 hrs using ABCC GRID Promoter TFSite.Comparison Page website.

Test Drug	Element	Site	Factor
ATRA	CAATP-1	CAATP-1	STAT
ATRA	CAATP-2	CAATP-2	STAT
ATRA	CAATP-3	CAATP-3	STAT
ATRA	CAATP-4	CAATP-4	STAT
ATRA	CAATP-5	CAATP-5	STAT
ATRA	CAATP-6	CAATP-6	STAT
ATRA	CAATP-7	CAATP-7	STAT
ATRA	CAATP-8	CAATP-8	STAT
ATRA	CAATP-9	CAATP-9	STAT
ATRA	CAATP-10	CAATP-10	STAT
ATRA	CAATP-11	CAATP-11	STAT
ATRA	CAATP-12	CAATP-12	STAT
ATRA	CAATP-13	CAATP-13	STAT
ATRA	CAATP-14	CAATP-14	STAT
ATRA	CAATP-15	CAATP-15	STAT
ATRA	CAATP-16	CAATP-16	STAT
ATRA	CAATP-17	CAATP-17	STAT
ATRA	CAATP-18	CAATP-18	STAT
ATRA	CAATP-19	CAATP-19	STAT
ATRA	CAATP-20	CAATP-20	STAT
ATRA	CAATP-21	CAATP-21	STAT
ATRA	CAATP-22	CAATP-22	STAT
ATRA	CAATP-23	CAATP-23	STAT
ATRA	CAATP-24	CAATP-24	STAT
ATRA	CAATP-25	CAATP-25	STAT
ATRA	CAATP-26	CAATP-26	STAT
ATRA	CAATP-27	CAATP-27	STAT
ATRA	CAATP-28	CAATP-28	STAT
ATRA	CAATP-29	CAATP-29	STAT
ATRA	CAATP-30	CAATP-30	STAT
ATRA	CAATP-31	CAATP-31	STAT
ATRA	CAATP-32	CAATP-32	STAT
ATRA	CAATP-33	CAATP-33	STAT
ATRA	CAATP-34	CAATP-34	STAT
ATRA	CAATP-35	CAATP-35	STAT
ATRA	CAATP-36	CAATP-36	STAT
ATRA	CAATP-37	CAATP-37	STAT
ATRA	CAATP-38	CAATP-38	STAT
ATRA	CAATP-39	CAATP-39	STAT
ATRA	CAATP-40	CAATP-40	STAT
ATRA	CAATP-41	CAATP-41	STAT
ATRA	CAATP-42	CAATP-42	STAT
ATRA	CAATP-43	CAATP-43	STAT
ATRA	CAATP-44	CAATP-44	STAT
ATRA	CAATP-45	CAATP-45	STAT
ATRA	CAATP-46	CAATP-46	STAT
ATRA	CAATP-47	CAATP-47	STAT
ATRA	CAATP-48	CAATP-48	STAT
ATRA	CAATP-49	CAATP-49	STAT
ATRA	CAATP-50	CAATP-50	STAT
ATRA	CAATP-51	CAATP-51	STAT
ATRA	CAATP-52	CAATP-52	STAT
ATRA	CAATP-53	CAATP-53	STAT
ATRA	CAATP-54	CAATP-54	STAT
ATRA	CAATP-55	CAATP-55	STAT
ATRA	CAATP-56	CAATP-56	STAT
ATRA	CAATP-57	CAATP-57	STAT
ATRA	CAATP-58	CAATP-58	STAT
ATRA	CAATP-59	CAATP-59	STAT
ATRA	CAATP-60	CAATP-60	STAT
ATRA	CAATP-61	CAATP-61	STAT
ATRA	CAATP-62	CAATP-62	STAT
ATRA	CAATP-63	CAATP-63	STAT
ATRA	CAATP-64	CAATP-64	STAT
ATRA	CAATP-65	CAATP-65	STAT
ATRA	CAATP-66	CAATP-66	STAT
ATRA	CAATP-67	CAATP-67	STAT
ATRA	CAATP-68	CAATP-68	STAT
ATRA	CAATP-69	CAATP-69	STAT
ATRA	CAATP-70	CAATP-70	STAT
ATRA	CAATP-71	CAATP-71	STAT
ATRA	CAATP-72	CAATP-72	STAT
ATRA	CAATP-73	CAATP-73	STAT
ATRA	CAATP-74	CAATP-74	STAT
ATRA	CAATP-75	CAATP-75	STAT
ATRA	CAATP-76	CAATP-76	STAT
ATRA	CAATP-77	CAATP-77	STAT
ATRA	CAATP-78	CAATP-78	STAT
ATRA	CAATP-79	CAATP-79	STAT
ATRA	CAATP-80	CAATP-80	STAT
ATRA	CAATP-81	CAATP-81	STAT
ATRA	CAATP-82	CAATP-82	STAT
ATRA	CAATP-83	CAATP-83	STAT
ATRA	CAATP-84	CAATP-84	STAT
ATRA	CAATP-85	CAATP-85	STAT
ATRA	CAATP-86	CAATP-86	STAT
ATRA	CAATP-87	CAATP-87	STAT
ATRA	CAATP-88	CAATP-88	STAT
ATRA	CAATP-89	CAATP-89	STAT
ATRA	CAATP-90	CAATP-90	STAT
ATRA	CAATP-91	CAATP-91	STAT
ATRA	CAATP-92	CAATP-92	STAT
ATRA	CAATP-93	CAATP-93	STAT
ATRA	CAATP-94	CAATP-94	STAT
ATRA	CAATP-95	CAATP-95	STAT
ATRA	CAATP-96	CAATP-96	STAT
ATRA	CAATP-97	CAATP-97	STAT
ATRA	CAATP-98	CAATP-98	STAT
ATRA	CAATP-99	CAATP-99	STAT
ATRA	CAATP-100	CAATP-100	STAT

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